REMARKS

Status of the Claims

Claims 1-3 and 5-29 were rejected. Claim 5 has been rewritten in independent form, incorporating the elements of claim 1 and therefore, will not require any additional searching. Upon entry of this amendment claims 1-3 and 5-31 will be pending.

As a preliminary matter, it appears that claims 30 and 31 added by amendment in Applicants' response filed January 6, 2003 have not been considered, even though the Office noted that the amendment was entered (see Office Action, page 2). Applicants believe that claims 30 and 31 are allowable.

Issuance of Final Rejection is Premature

The present Office Action, mailed on March 27, 2003 was made "Final" because allegedly "Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action." (Office Action, page 9). However, the amendments made in response to the previous non-Final Office action did ***not*** necessitate the new ground(s) of rejection. The new ground(s) for rejection, specifically the rejection under 35 U.S.C. § 112, first paragraph, could have been made in the previous office action and was not brought about by any amendment made by Applicants. Accordingly, Applicants respectfully request that the finality of the present Office Action be withdrawn.

In the previous Office Action (mailed October 4, 2002, Paper No. 10) the claims were rejected under 35 U.S.C. 112, second paragraph, for allegedly being indefinite. The claims were also rejected under 35 U.S.C § 102 and § 103. In the present Office Action, claims 1-3 and 5-8 stand rejected under 35 U.S.C. § 112, ***first*** paragraph, for allegedly not enabling *in vivo* methods. However, the rejection under 35 U.S.C. § 112, first paragraph, could have been made during the first Office Action. The amendment made to claim 1 in response to the previous Office Action merely incorporated the elements of originally filed claim 4 and corrected the grammatical and indefiniteness issues pointed out by the Office. The Amendment did ***not*** change the overall method of the claim nor did it

introduce new elements that were not present in the claims that were pending before the previous Office Action was issued.

As the M.P.E.P clearly states:

> Before final rejection is in order a clear issue should be developed between the examiner and applicant. To bring the prosecution to as speedy conclusion as possible and at the same time to deal justly by both the applicant and the public, the invention as disclosed and claimed should be thoroughly searched in the first action and the references fully applied; and in reply to this action the applicant should amend with a view to avoiding all the grounds of rejection and objection. Switching from one subject matter to another in the claims presented by applicant in successive amendments, or ***from one set of references to another by the examiner in rejecting in successive actions claims of substantially the same subject matter, will alike tend to defeat attaining the goal of reaching a clearly defined issue for an early termination,*** i.e., either an allowance of the application or a final rejection.

(M.P.E.P §706.07, emphasis added). The Office has done what the M.P.E.P explicitly states should not be done, "switching from one subject matter to another." Although the Office clearly could have made the rejection under 35 U.S.C.§ 112, first paragraph in the first Office Action, it did not and instead appears to be practicing piecemeal examination, which the M.P.E.P states should be avoided, "as much as possible" and further goes on to state that "The examiner ordinarily should reject each claim ***on all valid grounds available.***" (M.P.E.P § 707.07(g), emphasis added).

Accordingly, since the Office could have issued a rejection under 35 U.S.C § 112, first paragraph in the first Office Action because the claim amendments did not introduce new elements not already present in the pending claims and the method's scope (i.e. covering *in vivo* methods) did not change because of the amendment, the final rejection is premature.

In view of the foregoing, Applicants respectfully assert that the Final Rejection is premature and should be withdrawn.

Rejections under 35 U.S.C. § 112

Claims 1-3 and 5-8 stand rejected under 35 U.S.C. § 112, first paragraph, because allegedly the specification, while being enabling for an *in vitro* method of delivering a protein to a macrophage cell or a cell of macrophage derived lineage, does not reasonably provide enablement for an *in vivo* method.

Claims 9-29 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the present invention. The Office alleges that:

> An artisan of skill would have required undue experimentation to practice the claimed method because, while the claimed method is directed to delivery, the purpose of the method is for treatment and immunization and the art of *in vivo* gene therapy was unpredictable at the time of the art and the specification as filed does not provide sufficient guidance as to how an artisan of skill would have addressed the art recognized limitations and unpredictability of the method.

(Office Action, pages 2-3). The Office also alleges that any experimentation would be undue in performing the claimed invention. The Office attempts to support this argument by stating:

> Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by ***artisans of expertise.***

(Office Action, page 3). Applicants disagree.

Whether or not the USPTO has laboratory facilities to test the invention as claimed when working examples are not disclosed is irrelevant to whether the pending application satisfies the requirements under 35 U.S.C. §112, first paragraph. The Office is reminded that unless the Office supplies contradictory evidence, the Office ***must*** accept as true what is presented in the present application. A lack of working examples does not

indicate that an enablement rejection be automatically issued. Rather it is the overall state of the art at the time the invention was filed. Applicants respectfully disagree with the Office's characterizations of the overall state of the art as well as the rejection under 35 U.S.C. § 112, first paragraph.

Applicants respectfully assert that the Office misinterpreted the results of the Figures. The Office alleges that Figure 7 "is a diagrammatic representation of a plasmid called pNeZCD3alpah.1 [sic], however it is not clear as to what encoding sequence was used in this vector." Although the Office characterization of Figure 7is not clear, it appears that by stating "it is not clear as to what encoding sequence was used in this vector" the Office is referring to a nucleotide sequence that encodes a protein. If this is true, the protein that would be delivered using this type of DNA molecule is not limited to a particular protein, that is why a specific coding sequence is not disclosed. The Office is also reminded that the specific type of DNA molecule is not limited to what is shown in Figure 7. If Applicants' understanding is incorrect, Applicants respectfully request further clarification.

The Office also alleges that Figure 9 "compares differences in Nef mediated antibody production when Nef was under CMV promoter compared when under CD3 promoter. Looking as [sic] the figure, an artisan would think that there was no difference between CMV promoter and CD3 promoter." (Office Action, page 3). As a preliminary matter, Applicants acknowledge that the Office agrees with the Applicants that a macrophage specific promoter, such as the CD3 promoter, works just as well as the CMV promoter for producing an immune response. This working example demonstrates that administering a DNA molecule with a macrophage specific promoter, like CD3, gives similar results to those using a non-macrophage specific promoter, indicating that the invention as claimed works and is enabled. Whether the CD3 promoter works better than the CMV promoter is not relevant to the pending claims. The relevancy of Figure 9 is that it demonstrates that a macrophage specific promoter does work.

The Office also alleges that the specification

> lists genes whose promoters could be encompassed by macrophage specific promoter and the list includes all possible CD genes, chemokines, or molecules involved in the immune system... The specification does not provide any specific guidance or structure of these promoters, what sequences will be required for the promoter function, etc. In other words, an artisan would not know what parts of the promoter or what parts of the regulatory sequences to sue in making an expression vector. The specification does not provide any specific guidance as to what amount of plasmids or vectors will be administered, rather the specification does not provide any specific guidance to practice the claimed method.

(Office Action, page 4). The Office, therefore, alleges that a person of ordinary skill in the art would have to perform undue experimentation to make and/or use the claimed invention. Applicants respectfully disagree.

The specification provides adequate written description and enablement. A person of ordinary skill in the art could make/use the claimed invention without undue experimentation. The Office is reminded that experimentation is permissible if routine and, just because some experimentation may be required does not make it undue. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (M.P.E.P. § 2164.06). The present application provides a ***reasonable amount*** of guidance with respect to the direction in which the experimentation should proceed. The present specification outlines what promoters can be used. It is routine experimentation to determine what region of a gene comprises the promoter. A person of ordinary skill in the art would readily be able to take regions of a gene and perform experiments to determine which area(s) are part of the promoter. These types of experiments are nothing more than routine. The specification also teaches the amount of plasmids or DNA to be administered, see, for example, Examples 1 and 2 on pages 26-40 of the as filed specification and page 24, lines 1-11.

The Office also alleges that "one major issue is what vector will be used such that administration to a subject was effective and was able to deliver the vector to

macrophages. The specification does not provide any specific teachings as to what vectors will be suitable for this purpose." (Office Action, page 4). Applicants respectfully disagree.

Applicants have demonstrated in working examples the delivery of a protein to a macrophage cell or a cell of macrophage derived lineage (see, Examples 1 and 2). Furthermore, as stated in the specification:

> It is generally accepted that the majority of antigen in the blood is processed for antigen presentation in the spleen and antigens in tissue are transported and then processed and presented in the lymph nodes

(Specification, as filed, page 2, lines 14-16). Therefore, the protein that is produced by the DNA molecule will be delivered to a macrophage cell or a cell of macrophage derived lineage. Therefore, using the vectors described in the specification a person of ordinary skill in the art would be able to use the vectors or vectors made by those of ordinary skill in the art based on the teachings of the specification so that they are able to make and use the claimed invention.

As discussed above, the Office alleges that the overall state of the art is unpredictable and that this supports the Office's allegation that the claimed invention is not enabled. The Office cites several references in an attempt to support this argument. Applicants respectfully disagree with characterizations of the cited references.

According to the Office, Crystal (*Science* 270:404-410 1995, hereinafter "Crystal") allegedly assesses the state of the art of gene therapy at the time the claimed invention was made. Although Crystal does discuss gene therapy, Crystal does not comment on methods of delivering a protein to a macrophage cell or a cell of macrophage derived lineage of an individual by administering a DNA molecule. The technology discussed in Crystal is not same as the claimed invention. Therefore, conclusions reached by Crystal are not necessarily relevant to the present invention.

Anderson (*Nature* 392: 25-30, 1998) is also cited by the Office in an attempt to indicate that the claimed invention is not enabled. However, Anderson does not discuss the claimed invention. Anderson discusses gene therapy in the treatment of disease. The

pending claims, however, are directed to methods of delivering a protein to a cell, methods of delivering a protein to a lymph node, methods of inducing an immune response against an immunogen, methods of modulating an individual's immune system, methods of eliminating cells in a lymph node, and methods of delivering a desired protein to an individual wherein the protein is expressed in a macrophage cell and/or a cell of macrophage derived lineage. Therefore, conclusions reached by Anderson are not necessarily relevant to the present invention.

The Office also cites Clay *et al.* (Clark TM *et al. Pathology Oncology Research* 5:3-15, 1999, hereinafter "Clay") in an attempt to demonstrate that gene therapies to date have not been greatly successful and, according to the Office, Clay states, "Unfortunately, no gene therapy trial to date has been conclusively proven to be effective in treating the targeted disease..." (Office Action, page 5). Applicants respectfully assert that whether the claimed invention can be used to effectively treat a disease is irrelevant to the pending claims. Although the claimed methods may be used to treat diseases, such an element is not present in the claims. It appears that the Office is improperly importing limitations into the claims from the specification. Although, as discussed, the claims do not recite a method of treating a disease, the Office has nonetheless read this limitation into the claim. As the Courts have consistently stated, "limitations appearing in the specification ***will not be read into claims***, and ... interpreting what is meant by a word in a claim 'is not to be confused with adding an extraneous limitation appearing in the specification, which is improper.'" *Intervet Am., Inc. v. Kee-Vet Labs., Inc.*, 887 F.2d 1050, 1053, 12 USPQ2d 1474, 1476 (Fed. Cir. 1989), emphasis added.

The Office also alleges that the present invention is "clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest which results in a therapeutic effect." In support of this statement the Office cites Deonarain (*Expert Opin. Ther. Pat.*, Vol. 8, pages 53-69, 1998) and Verma (*Nature*, Vol. 389, 1997, pages 239-242). Although there may have been some reported difficulties in treating a specific disease, the Office has failed to provide a reference to support that the claimed invention

is not unpredictable. The present specification clearly demonstrates the effective delivery of a protein to a cell and induction of an immune response using the claimed invention (see, for example, Examples 1 and 2, and Figures 1-9). Whether the claimed invention is used for a specific therapeutic effect is up to the person of ordinary skill in the art using the claimed invention, but this limitation is not part of the pending claim. The pending claims do not recite minimum levels of protein expression or the duration of expression of a particular protein or how long any response should last

The Office is reminded that whether data is sufficient for a drug approval by the Food and Drug Administration is not the same as for patentability purposes. (See, M.P.E.P. 2164.05, "considerations made by the FDA for approving clinical trials are ***different*** from those made by the PTO in determining whether a claim is enabled", citations omitted, emphasis added). As discussed above it appears that the Office is improperly importing limitations into the claim, a practice that is strictly prohibited. Rather, the focus is on the language in the claims. The invention is encompassed by the claims is predictable and is enabled by the present specification.

Thus, the present application and the claimed invention is enabled and satisfies all requirements under 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 1-3 and 5-7 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Malik *et al.* (*Blood* 86:2993-3005, 1996, hereinafter "Malik"). The Office alleges that Malik discusses "a comparison of hematopoietic cell promoters to that of viral promoters, using retroviral vectors." (Office Action, page 7). Applicants respectfully disagree.

The standard for anticipation under 35 U.S.C. § 102(b) is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a

single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984).

Claim 1, the only independent claim rejected under 35 U.S.C. § 102 recites:

> A method of delivering a protein to a macrophage cell or a cell of macrophage derived lineage of an individual comprising the steps of:
>
> ***administering to said individual at a site on said individual's body, a DNA molecule*** comprising a nucleotide sequence that encodes said protein, wherein said DNA molecule is operably linked to a macrophage specific promoter and a polyadenylation signal that are functional in a macrophage cell and/or a cell of macrophage derived lineage, wherein said DNA molecule is taken up by a macrophage cell and/or a cell of macrophage derived lineage where said nucleotide sequence is expressed to produce said protein in said macrophage cell and/or said cell of macrophage derived lineage.

(emphasis added).

According to claim 1, what is administered is a DNA molecule to the individual. Malik discusses retroviral-mediated gene expression in human myelomonocytic cells comparing hematopoietic cell promoters to viral promoters. Malik discusses infecting cells with a retrovirus produced by a packaging cell line. (see, Malik *et al.*, page 2994 under "Materials and Methods"). A retrovirus is defined as "A family of small viruses with ***RNA*** genomes of 5,000-10,000 nucleotides." (*The Language of Biotechnology: A Dictionary of Terms*, 2ed. Washington 1995, copy attached). Malik does ***not*** teach or even suggest delivering a protein to a cell by administering a DNA molecule. Furthermore, Malik does not teach administering any agent, RNA or DNA, to an "individual at a site on the individual's body." Malik also fails to teach or even suggest a method of delivering a protein to a macrophage cell or a cell of macrophage derived lineage of an individual comprising a step of administering to the individual at a site on the individual's body, a DNA molecule comprising a nucleotide sequence that encodes the protein. Thus, Malik clearly does not disclose each limitation of the claims and therefore cannot anticipate the present invention.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1-3 and 5-8 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Malik *et al.* in view of Dropulie *et al.* (U.S. Patent No. 5,887,767), Kataoka *et al.* (*Journal of Biological Chemistry* 272:18209-18215, 1997, hereinafter "Kataoka") and Horvai *et al.* (*PNAS* 92:5591-5393, 1995, hereinafter "Horvai"). Applicants respectfully disagree.

The Office suggests, it would have been obvious for an

> artisan of ordinary skill to modify the vectors of Malik *et al.* by substituting the promoters of CD156 gene, scavenger receptor gene or any other macrophage cell specific promoters with a reasonable expectation of success. An artisan of skill would have [*sic*] motivated to modify the vector to find the best promoter that will allow specific expression in macrophages and could be used for delivering genes to atherosclerotic tissues or cells. Additionally, an artisan could modify the vector for making conditional vectors for expressing toxins as taught by Dropulie *et al.*

(Office Action, page 9).

The Office alleges that Malik discusses a comparison of hematopoietic cell promoters to that of viral promoters, using retroviral vectors. However, as discussed above, Malik fails to recite or even suggest the delivery a protein to an individual using a DNA molecule. In addition to the deficiencies discussed above, the Office admits that Malik "does not teach promoters of scavenger receptor or CD156 reporter." (Office Action, page 8).

Horvai discusses scavenger receptor A gene regulatory elements that target gene expression to macrophages and to foam cells of atherosclerotic lesions. However, the Horvai reference does not cure the deficiencies of Malik. Horvai fails to teach or even suggest a method of delivering a protein to an individual by administering a DNA molecule. Horvai, on the other hand discusses placing the promoter of the scavenger receptor A gene in a transgenic mouse to study the expression pattern driven by this

promoter. Nowhere does Horvai discuss delivering a protein to an individual at a particular site by administering a DNA molecule.

Kataoka discusses the structure of the murine CD156 gene and the characterization of its promoter and chromosomal location. However, Kataoka fails to cure the deficiencies of Malik and Horvai. Kataoka does ***not*** teach or even suggest a method of delivering a protein to an individual by administering a DNA molecule.

Dropulie does not cure the deficiencies of Malik, Horvai, and Kataoka. Dropulie discusses a conditionally replicating viral vector to express a gene. Dropulie discusses an providing a conditionally replicating viral vector. (Abstract, line 1). Dropulie defines a conditionally replicating viral vector as "a virus (which preferably is the same type of virus as the infection being treated) that replicates only upon complementation with a wild-type strain of virus or when wild-type virus infects cells containing conditionally replicating vector genome," (Col. 10, lines 9-13). Dropulie does not discuss administering DNA using a macrophage specific promoter. Additionally, the Dropulie does not discuss selecting a lymph node as is disclosed in claim 9.

In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the Examiner to provide a reason why one of ordinary skill in the art would have been led to modify a prior art reference or to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. Apages Int. 1985). To this end, the requisite motivation must stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and not from appellants' disclosure, see for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. Apages Int. 1992). In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. Apages 1993), is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available

> to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent Applicants' invention without also providing evidence of the motivating force that would **impel** one skilled in the art to do what the patent Applicants have done. (citations omitted; emphasis added)

Significantly, the Office Action identifies no "motivating force" that would "impel" persons of ordinary skill to modify the respective teachings of the cited references and achieve the claimed invention.

Rather, the Office Action makes a general statement that it would be obvious to combine teachings of a reference discussing a particular retroviral vector with a reference that discusses a specific promoter. Such a generalized motivation is **not** a "motivating force" that would "impel" persons of ordinary skill to modify the respective teachings of the cited references and achieve the claimed invention. Such a statement, at most, raises an inappropriate "obvious to try" standard. Indeed, the court made it clear that it is improper to reject claims as "obvious to try" where the motivation to combine references arises merely because the subject matter of the claimed invention is a promising field for experimentation, although the prior art provides only general guidance as to particular form of the claimed invention or how to achieve it. *In re O'Farrell*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). Without more specific suggestions in the prior art, there is insufficient motivation to combine the cited references. Furthermore, "focusing on the obviousness of substitutions and differences, instead of the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Son*, 16 U.S.P.Q.2d 1923, 1927 (Fed. Cir. 1990).

Therefore, the Office has failed to show any motivation as to why a person of ordinary skill in the art would combine the references Malik, Dropulie, Kataoka, and Horvai. There is nothing in any of the references that would "impel" one of ordinary skill in the art to make the combination. The Office has failed to show that a person of ordinary skill in the art would have an expectation of success based on the combination

of the references. The Office only uses the general statement that there would have been "a reasonable expectation of success." The Office provides no specific reason or evidence as to ***why*** a person of ordinary skill in the art would have an expectation of success. Again, as discussed above, the references would not "impel" one of ordinary skill to make the combination and/or modify the references to obtain the claimed invention. The Office has used nothing more than generalizations to combine the references, which is improper.

In addition, it appears that the only motivation that the Office is using to combine the references is the use of the Applicants' specification and hindsight reconstruction, which is strictly forbidden. *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."). When assessing whether or not a combination of references would have produced a claimed invention, one must consider the teaching of each reference as a whole without undue emphasis on those features that would support a finding of obviousness. *In re Wesslau*, 147 U.S.P.Q. 391 (C.C.P.A. 1965) (it is impermissible to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the references fairly suggest to one of ordinary skill in the art).

Consideration of the cited references as a whole for what they each fairly suggest, demonstrates that a person of ordinary skill seeking to combine them would not have produced any claimed invention. In this respect, the Office Action has apparently picked one particular element from Malik, one particular element from Dropulie, one particular element from Kataoka, and one particular element from Horvai. One skilled in the art, however, would ***not*** be motivated to pick and choose only those specific elements referred to in the Office Action from the many elements recited in the references and combine the selected elements in the specific manner indicated in the Office Action. Indeed, it appears that the only guide to picking and choosing particular elements from the cited art of records appears to have been the present application. Thus, the combination of references is improper for, at the very least, failure to provide motivation

to combine references and for its use of hindsight reconstruction based upon Applicants' disclosure.

The Federal Circuit has recently affirmed the requirement for motivation to combine references, stating that:

> virtually all [inventions] are combinations of old elements. Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed [**10] elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention . . .
>
> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and ***with no knowledge of the claimed invention***, would select the elements from the cited prior art references for combination in the manner claimed . . .
>
> To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

Yamanouchi Pharm. Co. v. Danbury Pharm, Inc., 231 F.3d 1339 (Fed. Cir. 2000); 56 U.S.P.Q.2D 1641, 1645, citing *In re Rouffet*, 149 F.3d 1350, 1357-58, 47 USPQ2d 1453, 1457-8 (Fed. Cir. 1998) (emphasis supplied).

It appears that the Office has done what Yamanouchi reaffirms should not be done -- used Applicants' specification as a blueprint.

However, even if the Office has provided motivation to combine the cited references, which it has not, the combination of the references does not yield the claimed invention. Rather, if one were to combine the references one would be left with a retroviral vector with an RNA genome and/or a conditionally replicating virus, not a DNA molecule as is required by the pending claims. None of the references alone or in combination discuss or even suggest a method of delivering a protein to a macrophage

cell or a cell of macrophage derived lineage of an individual comprising the steps of: administering to the individual at a site on the individual's body, a DNA molecule comprising a nucleotide sequence that encodes the protein, wherein the DNA molecule is operably linked to a macrophage specific promoter and a polyadenylation signal that are functional in a macrophage cell and/or a cell of macrophage derived lineage, wherein the DNA molecule is taken up by a macrophage cell and/or a cell of macrophage derived lineage where the nucleotide sequence is expressed to produce the protein in the macrophage cell and or the cell of macrophage derived lineage.

Furthermore, there is no motivation to modify the references to obtain the claimed invention because there can be no expectation of success when looking at the references in their entirety. A person of ordinary skill in the art would not expect that a method used for a retroviral vector and/or virus would work for the administration of a DNA molecule. RNA and DNA have different chemical properties, among which are that RNA is single stranded and is generally less stable than DNA. Additionally, a virus encloses its genome in a protective barrier, which can have an impact on whether the viral genome is able to function properly. Therefore, the references cited in the Office Action would not provide the necessary motivation to "impel" a person of ordinary skill in the art to modify the references because there would be no expectation of success since the molecules are different from the administered DNA molecule of the claimed invention. As discussed above, it appears that the only suggestion to obtain the claimed invention is the Applicants' specification, which is strictly prohibited.

Even though, Applicants respectfully assert that the Office has failed to establish a *prima facie* case of obviousness, in order to further prosecution Applicants have amended claim 5 so that it is independent. As discussed above, the references cited by the Office either alone or in combination fail to render claim 5 obvious. The references do not suggest or motivate one of ordinary skill in the art to modify the references to obtain the claimed invention. Furthermore, even if the references were combined they would not yield the claimed invention.

Thus, in view of the foregoing, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness. In particular, the Office has failed to provide any motivation that would ***impel*** one skilled in the art to modify and/or combine the cited references so as to produce Applicants' claimed invention.

Accordingly, Applicants respectfully request the rejection under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

Applicant believes the claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicant invites the Examiner to contact the undersigned at (215) 665-6928 to clarify any unresolved issues raised by this response.

Attached hereto: A copy of page 239 of *The Language of Biotechnology: A Dictionary of Terms*, 2ed. Washington 1995.

Respectfully submitted,

Date:
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